Assessment of Exposure to Lead and Cadmium through Biological Monitoring: Results of a UNEP/WHO Global Study[1]

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This paper describes a UNEP/WHO project on the assessment of human exposure to lead and cadmium through analysis of blood and kidneys. The following countries have participated: Belgium, India, Israel, Japan, Mexico, People's Republic of China, Peru, Sweden, United States, and Yugoslavia. No laboratory started the monitoring before achieving satisfactory results of quality control (QC) analysis (samples of cow blood spiked with lead and cadmium and freeze-dried horse kidney cortex for cadmium analysis) according to predetermined criteria based on a linear regression model. Two hundred teachers from one urban area in each country constituted the target group for lead and cadmium in blood and cases of "sudden, unexpected death" for cadmium in kidney cortex. QC samples were analyzed in parallel with the monitoring samples to assure validity of the obtained results. The quality assurance program also included preanalytical quality control. There was considerable variation in metal exposure between areas. Geometric means for *lead in blood* ranged from about 60 μg Pb/liter in Beijing and Tokyo to 225 in Mexico City. The values were below 100 μg Pb/liter also in Baltimore, Jerusalem, Lima, Stockholm, and Zagreb, and between 100 and 200 μg Pb/liter in Brussels and India. In general, males had higher blood levels than females and smokers higher than nonsmokers. With a few exceptions the values were lower than results reported in a recent study within the European Communities. Geometric means for *cadmium in blood* ranged from 0.5 μg Cd/liter in Stockholm and Jerusalem to 1.2 in Brussels and Tokyo. Cadmium levels were considerably higher among smokers than among nonsmokers. Tokyo had the highest values for *cadmium in kidney cortex* with a geometric mean in the age group 40–60 years of 60–70 mg Cd/kg wet wt. Lowest values were found in Baltimore, Beijing, India, and Jerusalem, with means around 20–25 mg Cd/kg wet wt. There was a tendency toward higher values for smokers than for nonsmokers, but no differences related to sex. Data were not received from Mexico and Peru.

INTRODUCTION

This paper describes the results of a three-year global UNEP/WHO pilot project on assessment of human exposure to lead and cadmium through biological monitoring. It has been carried out within the framework of UNEP's Global Environmental Monitoring System (GEMS). Major objectives of the project have been to carry out studies on exposure to lead and cadmium among selected segments of the population in a number of countries with different climate and development and to design and implement a program for rigid quality control in con-

[1] Participants in the project are listed at the end of the report.

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nection with sampling, storage, transport, and analysis. Lead and cadmium have been determined in blood to give an estimate of recent exposure. Cadmium has also been measured in kidney cortex to evaluate long-term accumulation.

The following countries have participated: Belgium, India, Iran (only in the initial phase), Israel, Japan, Mexico, People's Republic of China (hereinafter referred to as China; from May 1981), Peru, United States, and Yugoslavia. The scientific responsibility for the implementation of the project was delegated to a coordinating institution (CI), the National Institute of Environmental Medicine and the Department of Environmental Hygiene of the Karolinska Institute, Stockholm, Sweden. A complete report has been prepared for UNEP/WHO (Vahter, 1982).

The project was divided into two main phases. The first was devoted primarily to training and technical assistance to the participating institutions. The second was devoted to the actual monitoring of lead and cadmium with an integrated quality control program. Developing countries participating in the project were supported by the supply of additional equipment. The main resources in the program, however, were provided by the national institutions themselves.

The Rationale for Assessing Human Exposure to Lead and Cadmium through Biological Monitoring

A large part of the blood cadmium is related to recent exposure. Under long-term low-level exposure the concentration in blood is therefore a useful indicator of the exposure during recent months. The half-time in blood is estimated to be 2–3 months. If the exposure levels do not undergo major changes, blood levels may be used also for the evaluation of long-term risks (WHO, 1980b). Cadmium has a biological half-time in the human body of about 20 years and the main site of accumulation at long-term low-level exposure is the kidneys. For a detailed discussion of metabolic models for cadmium reference is made to Friberg *et al.* (1974), Kjellström and Nordberg (1978), and Cannor *et al.* (1979).

About 90% of the total body burden of lead is present in the bones and teeth, as a stable fraction, which is not accurately indicated by the blood lead level. In blood 95% of the lead is bound to the erythrocytes. The blood lead level reflects a dynamic equilibrium between exposure, absorption, distribution, and elimination of lead (WHO, 1980b) and is probably the best indicator of current exposure.

The Need for Quality Control

It was recognized at an early stage in the planning that there was a great need for strict quality control procedures in the monitoring of trace elements in biological media. For example, mean concentrations of lead in blood in the general population of 400–500 μg Pb/liter have been reported also during recent years without any quality control (Secchi and Alessio, 1974; Aggarwal *et al.*, 1979; Khan *et al.*, 1980; Khera *et al.*, 1980). Similarly, for cadmium mean values of 20–200 μg Cd/liter have been reported (von Mertz *et al.*, 1972; Hecker *et al.*, 1974; Sumino *et al.*, 1975; Mishima, 1976). In such cases the accuracy of the data has to be questioned. The situation is much more difficult to evaluate when reported concentrations are within a range which is not unrealistic, but where there is no guarantee that a quality assurance program has been implemented. Unfortunately, most published reports fall into this category.

Results from several interlaboratory comparisons further amplify the need for quality control (Keppler *et al.*, 1970; Donovan *et al.*, 1971; Berlin *et al.*, 1973; Browne *et al.*, 1974; Lerner, 1975; Lauwerys *et al.*, 1975; Paulev *et al.*, 1978; Boone *et al.*, 1979; Maher *et al.*, 1979). The studies show that the accuracy and precision of trace metal analysis in biological specimens in general appear to be unsatisfactory. This may also hold for laboratories that have gained considerable experience by analyzing a large number of biological samples over many years.

Although a large number of studies from different countries have aimed at evaluating "normal" levels of lead and cadmium in the general population, there are very few international studies. One on lead, from the middle of the 1960 decade (Goldwater and Hoover, 1967), was sponsored by WHO. All analyses were performed with one single method "a standard dithizone method," at a recognized laboratory in the United States. No quality assurance data were, however, reported either for the analyses or the sampling. There is also one recent European study on lead in blood by the Commission of the European Communities (CEC, 1981; Berlin, 1982), based on a Council Directive of March 29, 1977. In this study a quality assurance program was implemented and close collaboration between the UNEP/WHO project and the CEC program was established.

METHODS

Quality Control: Design

The analytical quality control (QC) involved analysis of both internal quality control samples (IQC, concentrations of metals known to the laboratories) and external quality control samples (EQC, concentrations not known to the laboratories). The QC samples for the analyses of lead and cadmium consisted of cow blood spiked with different concentrations of the metals. For the analysis of cadmium in kidney cortex, samples of freeze-dried horse kidney cortex were used.

During the training phase the laboratories received 12 sets of EQC samples to be analyzed together with the IQC samples. The results were evaluated at CI and the laboratories received a feed-back, usually via telex, in the form of "true" values (reference values), and information on whether or not the results met predetermined criteria for acceptance. The QC sets consisted of at least six blood samples and four kidney cortex samples.

It was agreed that analysis of blood and kidneys from the target populations should not start until results from the training phase were satisfactory according to certain criteria. Quality control during the actual monitoring phase was based on five QC sets to be analyzed together with about 200 blood samples and three QC sets to be analyzed together with about 50 kidney cortex samples.

Quality control did not concern only the accuracy of the analytical performance but took also into consideration questions relating to sampling and avoidance of contamination (preanalytical quality control). Evacuated blood collection tubes

(Venoject, Terumo Corp., Tokyo, Japan) with heparin from one and the same batch were provided by the CI after control of the metal content. Before collecting blood, the skin was carefully washed and cleaned with disposable napkins, saturated with 70% isopropyl alcohol (Medi-Swab, Pharmax Limited, Bexley, U.K.), provided by CI after check for metal content. Written instructions for the sampling of blood were worked out and a demonstration was made at the CI during a meeting in Stockholm in May 1980 (WHO, 1980a).

The risk of significant contamination was considered less pronounced for kidney cortex samples due to the higher concentrations of cadmium in the kidneys compared to blood. To avoid contamination to the greatest possible extent and to get comparable samples, the laboratories received a film showing procedures for collection of kidney cortex samples at autopsies. The film was produced by WHO/IAEA in relation to the project "WHO/IAEA Joint Research Programme on Trace Elements in Cardiovascular Diseases (Autopsy Studies)" (Masironi and Parr, 1979).

Quality Control: Samples

Quality control samples should be as identical as possible to the actual monitoring samples and should contain comparable concentrations of lead and cadmium. No suitable standard reference material was commercially available for blood and kidneys. Blood samples of human or bovine blood with EDTA as anticoagulant, hemolyzed by ultrasonication, and sterilized by gamma irradiation have been used within the CEC programme (Yeoman and Berlin, 1979). The stability of lead in the blood was studied and found satisfactory (WHO, 1979). The QC samples in the UNEP/WHO project had to meet certain criteria. They had to be stable over long periods of time and withstand transport from the CI to the participating laboratories in different parts of the world. Transport could last more than 24 hr and outside temperatures could reach 30–40°C. The QC samples had to be sterilized to facilitate custom clearance.

The possibility of using freeze-dried blood spiked with the metals was considered, since such samples would be less sensitive to temperature variations than liquid blood. Preliminary studies both at the CI and within CEC, however, indicated problems in the reconstitution of the blood. Furthermore, freeze-dried samples would require distribution of deionized water or buffer solutions, free of metals, to the laboratories in order to minimize the possibilities of contamination at the reconstitution step. It was therefore decided to use blood as such without freeze-drying. It was felt necessary to make a thorough study on the influence of different environmental factors. This was considered particularly important for cadmium in blood as virtually no information existed which could be used directly for the project. In the full report, results from these studies are given (Vahter, 1982). The following procedures were decided on for preparation and dispatching of quality control samples.

To cow blood, collected at a slaughterhouse, was added EDTA (dipotassium salt), in an amount giving a final concentration of 1.5 mg EDTA/ml. The blood was ultrasonicated for hemolyzation. Less than 1% of the original red cells remained after ultrasonication. The blood was centrifuged to remove cell debris. Thereafter,

cadmium nitrate and lead nitrate in deionized water were added to the blood. No changes of cadmium concentrations in blood took place during an observation period of 8 months as judged from studies with radioactive cadmium. For the major part of the project blood was dispensed in 5-ml acid-washed polypropylene tubes with screw-on caps. After dispensing, the samples were sterilized by gamma irradiation (total dose of 2.5 Mrad) and stored deep-frozen at the CI. Since the stability tests had shown that the blood may clot at temperatures above +30°C, the samples were packed with ice in neopolyene containers for the transport to the laboratories. With four cooling blocks, each of about 600 g, and the containers kept at about +20°C, the inside temperature remained below +5°C for 48 hr and below +10°C for 72 hr. All samples were sent air freight.

Since cadmium was to be analyzed also in kidney cortex, the NBS standard reference material bovine liver was distributed to the laboratories in the beginning of the training phase of the project. It has a matrix similar to that of kidneys, but the main disadvantage for use as QC samples is that the concentration of cadmium is much lower than normally found in kidney cortex. Furthermore, bovine liver is available only with one concentration of cadmium whereas for quality control purposes different concentrations of cadmium were required.

Horses accumulate cadmium in the kidney cortex to an even greater extent than humans (Piscator, 1976). By selecting kidneys from horses of different ages at slaughterhouses, it was possible to obtain kidney cortex samples with varying concentrations of cadmium. Deep-frozen kidneys were thawed and the cortex was separated from the medulla and cut into 5-mm pieces. These were deep-frozen in liquid nitrogen. Homogenization was performed by liquid nitrogen grinding in a cryogenic grinding machine (Spex Industries, Inc., N.J.). The ground material was freeze-dried and thoroughly mixed. It was kept in desiccators before dispensing in 5-ml polypropylene tubes, previously washed in diluted nitric acid and deionized water. The samples were thereafter sterilized by gamma irradiation (2.5 Mrad) and stored at room temperature. The homogeneity was checked by analysis of a large number of subsamples, showing a coefficient of variation of about 2%.

The true concentrations of lead and cadmium in biological tissue are not yet possible to determine. The best estimation is probably attained with the Isotope Dilution/Mass Spectrometry (IDMS) method carried out in "ultra-clean" facilities (Barnes *et al.*, 1973; Facchetti, 1978; Everson and Patterson, 1980). The "true" levels were determined with the assistance of the U.S. National Bureau of Standards (NBS) and the CEC Joint Research Centre, Ispra, Italy (ISPRA). IDMS is expensive both in time and cost per assay, and it was possible to get assistance only on a limited scale and at a rather late stage of the project. Lead analyses for reference purposes were performed also using atomic absorption spectrophotometry at ISPRA and at the Regional Toxicology Laboratory (RTL), Dudley Road Hospital, Birmingham, U. K. (where the QC samples for the CEC program were prepared).

The major problems with decisions on "true" values were related to the levels in unspiked blood. Estimations of the "true" values for unspiked blood were based on analyses of unspiked as well as spiked samples. This also made it possible to calculate the recovery of added lead and cadmium. The basic lead level in unspiked

bovine blood was initially estimated to be 24 μg Pb/liter. The mean value for analyses at the CI and at the reference laboratories was 25 μg Pb/liter. The mean recovery for the different laboratories and methods was approximately 100%.

The cadmium level for unspiked bovine blood was originally estimated to be 0.2 μg Cd/liter. Later analyses indicated that the basic level might have been slightly higher. The mean values at CI (AAS) and NBS (IDMS) were 0.3 and 0.4 μg Cd/liters, respectively. In their comments NBS stated that their cadmium analyses were not as reliable as their lead analyses because of the presence of high and varying blanks. NBS estimated that this introduced an uncertainty of about 0.2 μg Cd/liter. At NBS an experiment was done to determine whether cadmium had been adsorbed to the container walls. No cadmium above the analytical blanks was found in the container walls after the blood was taken out, indicating that the container material and the storage conditions were satisfactory. The observations confirmed the results of the stability tests with radiolabeled cadmium carried out at the CI.

True values for cadmium in kidney cortex were determined with the assistance of the International Atomic Energy Agency (IAEA), Vienna, Austria, the Kernforschungsanlage in Jülich, Federal Republic of Germany, and the Interuniversity Reactor Institute in Delft, the Netherlands, all using neutron activation analysis (NA). The CI also arranged for neutron activation analysis at the Tekniska Röntgencentralen (TRC), Stockholm, Sweden. At the CI kidney cortex was analyzed with a conventional flame AAS method. On the average there was good agreement. The mean ratio between results of AAS analyses and results of NA analyses was 1.04 with a standard error of 0.009 ($n = 23$). Detailed results of the reference analyses are given in the full report (Vahter, 1982).

Quality Control: Statistical Procedures and Criteria for Acceptance of Laboratory Performance

Results for each set of QC samples from a participating laboratory were statistically assessed in order to decide whether to accept or reject the laboratory's current performance. The main purpose was to guard against systematic errors. In a diagram where y is the reported value and x is the "true" value, a recovery of 100% would correspond to a straight line through the origin and a regression of unity, i.e., $y = x$. One appropriate way of expressing a laboratory's performance is to calculate a regression line of the reported versus the "true" values—which can be thought of as an average of the current performance—and to establish an acceptance criterion based on how much the line may deviate from the ideal $y = x$. This procedure has been employed since it lends itself to making probability statements in terms of statistical power. It was considered necessary to allow for somewhat higher deviation, as a proportion of x, at the lower x range than at the higher. The limits for maximum allowable deviations (MAD lines) from the regression line $y = x$ were set as follows:

for lead in blood (μg/liter), $y = x \pm (0.1x + 20)$;
for cadmium in blood (μg/liter), $y = x \pm (0.1x + 1)$;
for cadmium in kidney cortex (mg/kg dry wt), $y = x \pm 0.15x$.

One basic parameter in the power calculation and hence in the quality control procedure is the random error of the method which can be estimated from each set of quality control results. Experience showed that the error of method centered around 10 μg/liter for lead in blood, around 0.5 μg/liter for cadmium in blood, and around 3.0 mg/kg dry wt for cadmium in kidney cortex in well-established laboratories. It was judged as more appropriate to use these average values than to depend on estimates made each time since each quality control set consisted of 4–6 samples only. Using the average error estimation based on past experience instead of an unusually high current error may lead to an undue acceptance of the regression line. This is, however, quite rare and requires that the individual large deviations cancel out or else the line will certainly deviate to such an extent that the QC results will be rejected.

In the following a short account is given of the procedure used for acceptance of a quality control set. More detailed descriptions are given in the full report (Vahter, 1982) and in a working paper by Cederlöf for the 1980 Stockholm meeting (Cederlöf, 1980).

Spiking of blood samples delivered to the laboratories ranged as a rule between 100 and 400 μg/liter in the case of lead, and between 1 and 15 μg/liter for cadmium. Cadmium in kidney cortex samples usually varied between 50 and 400 mg Cd/kg dry wt. The table below gives an account of the outcome of an assumed set of quality control analyses together with the reference values (μg Pb/liter).

x (reference values)	100	160	220	280	340	400
y (reported values)	113	151	203	287	343	386

Calculation of the regression line reveals the function $y = 0.9643x + 6.095$. The regression line and the two MAD lines are shown in Fig. 1.

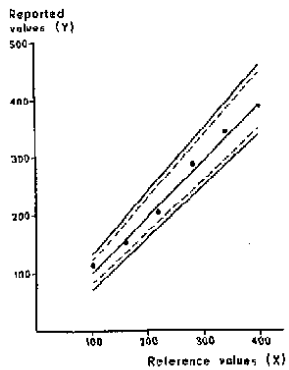


FIG. 1. Regression line based on six reported values. The solid lines indicate the MAD lines and the dotted lines the acceptance lines. (For explanation, see text.)

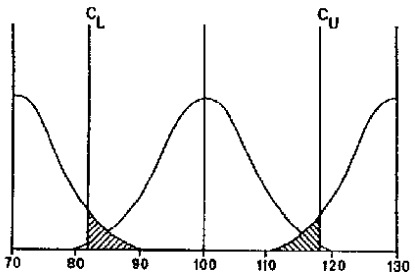


FIG. 2. Hypothetical normal distribution curve of function value corresponding to $x = 100$, the ideal ($y = x$) relationship, and distribution curves corresponding to function values of two MAD lines with mean of 70 (lower) and 130 (upper). (For further explanation, see text.)

For closer scrutiny any arbitrary point along the regression line may be chosen, e.g., the point corresponding to $x = 100$, which was chosen as the lower evaluation point. The line has here the function value

$$\hat{y}_{100} = 0.9643 \cdot 100 + 6.095 = 102.52.$$

Like all sample statistics also $\hat{y}_{100}$ has a sampling error, $\sigma_{\hat{y}}$, which is a function of

n = number of observations (6),
d = difference between x value and x mean (100 − 250 = −150),
σ_x = standard deviation of x values (112.25),
$\sigma_{y|x}$ = error of method (12.9; in the acceptability calculations assumed to be 10.0), such that

$$\sigma_{\hat{y}}^2 = \sigma_{y|x}^2\left(\frac{1}{n} + \frac{d^2}{(n-1)\cdot\sigma_x^2}\right) = 10^2\left(\frac{1}{6} + \frac{(-150)^2}{(6-1)\cdot 112.25^2}\right) = 52.4.$$

The square root of this quantity, $\sigma_{\hat{y}}$, is often named "operating error" and equals 7.24. The operating error is the same also for the function of another x value along the range, namely for $x = 400$, which is just as much above the x mean (250) as 100 is below and was chosen as the upper evaluation point.

The philosophy behind the power calculation that determines the probability of excluding an unsatisfactory laboratory is revealed by Fig. 2. Three normal distributions are indicated in the chart, one with mean 70 (the function value of the lower MAD line), another with mean 100 (the ideal line), and a third with mean 130 (the upper MAD line). Of the two extreme curves each has one tail (shaded) between the vertical lines named C_L and C_U. The shaded tail occupies only 5% of its own curve. This implies that if the observed function value falls between C_L and C_U there is very low probability that it belongs to a true line with true function value of 70 or lower or a true line with true function value of 130 or higher, which are the two points specified by the MAD lines. The probability that an empiric function value within the interval C_L–C_U should belong to either the left or the right probability curve is in fact 10% only, implying that a test so constructed has a power of 100 − 10 = 90%. According to probability theory the line C_L cuts the abscissa at a point corresponding to 1.645 times the operating error to the right of the mean 70, and correspondingly, that the intersection of line C_U with the abscissa is 1.645 times the operating error left of the mean 130. Accordingly, the acceptance interval lies between

$$70 + 1.645 \cdot 7.24 \quad \text{and} \quad 130 - 1.645 \cdot 7.24,$$

thus between 81.9 and 118.1.

Exactly the same calculations can be performed for the upper evaluation point ($x = 400$) giving the interval 351.9–448.1.

Target Populations

Ideally, the target population for assessment of lead and cadmium in blood would be a random sample of urban or rural populations without any further restrictions. However, in some countries it would be difficult to find a limited group of persons representing the general population, even for a limited area. An alternative approach was to study certain occupational groups not extensively exposed to lead and cadmium. For this project teachers were chosen as target population. They would constitute a rather homogeneous group and enable reasonable comparisons between countries. They would be fairly easy to select from lists in the chosen cities and areas, and the samples could probably be collected at the working places without any particular risk of contamination. Another advantage of choosing teachers was that they represent some form of middle class and both sexes would be represented.

About 200 full-time employed elementary school teachers from one urban area in each country constituted the target population for the monitoring of lead and cadmium in blood. Data to be reported to the CI included area where the schools were located, sex, date of birth, smoking habits, date of sampling, date of analysis, and lead and cadmium concentrations in blood (μg/liter). A detailed recommendation on methods on how to select the teachers was worked out for the project by Carra (1980).

Certain chronic diseases such as cancer may change the cadmium distribution in the body (see, e.g., Friberg *et al.*, 1974). It was therefore decided that the target population for determination of cadmium levels in kidney cortex should consist of cases of "sudden unexpected death" without any obvious kidney disease. Samples of kidney cortex from about 50 subjects were to be collected at autopsy with as wide an age range as possible covered. Data to be reported to the CI included area of residence, sex, date of birth, smoking habits, underlying and contributing cause of death, date of sampling, date of analysis, and cadmium concentrations in kidney cortex.

RESULTS

Training Phase

The improvements made during the training phase, and documented below,

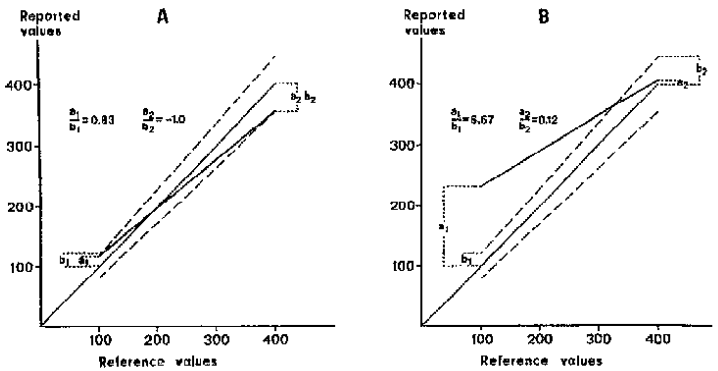


FIG. 3. Illustrations of the procedure used for the calculation of ratios between obtained deviation from the reference value and the accepted deviation at the preset evaluation points (100 and 400 μg/l). For explanation, see text. (A) An example of an accepted QC run; (B) a rejected QC run.

were partly the result of an increased awareness within the participating laboratories themselves, based on the outcome of the QC analyses. The analytical capability at several of the laboratories also improved considerably through repeated visits by a consultant from the CI (Birger Lind, research engineer), as well as training at the CI and other laboratories.

In order to obtain a quantitative estimate of results of lead and cadmium in blood among different QC runs, ratios were formed on the basis of the following calculations. The difference between the function values at each evaluation point and the "true" values (the value on the regression line $y = x$) were divided by the accepted deviation at the evaluation points. The procedure is illustrated in Fig. 3. The calculations can be expressed as

$$a_1/b_1 \quad \text{and} \quad a_2/b_2,$$

where a_1 and a_2 in Fig. 3 indicate the differences between the end points of the calculated regression line and the "true" values, and b_1 and b_2 indicate the accepted deviation from the "true" value (differences between the acceptance lines and the "true" values).

The calculated ratios have been indicated as bars. Figures 4 and 5 show the overall results for lead and cadmium, respectively. The left bar of each pair represents the ratio at the lower evaluation point (x = 100 μg Pb/liter and x = 1.5 μg Cd/liter), while the right bar of each pair represents the upper evaluation point (x = 400 μg Pb/liter and x = 12 μg Cd/liter). The maximum allowable ratio for acceptance is 1. Negative ratios indicate that the results obtained are lower than the reference values, while positive ratios indicate results higher than the reference values. The height of the bar gives an estimate of how much reported results

deviate from the reference values at the evaluation points. The numbers of the quality control runs do not correspond to a common time point during the project.

Lead in blood. Figure 4 shows that there was only one laboratory which met the criteria for acceptance throughout the training phase. In general, deviations from the reference values were most notable during the first quality control runs. The results improved significantly with time as shown by lower ratios.

Cadmium in blood. Figure 5 shows that none of the laboratories met the criteria for acceptance in all QC runs. The situation in the initial phase of the project was in general worse than for lead in blood. Most of the laboratories had no or limited experience in cadmium analysis at the start of the program. Eventually all laboratories met the criteria for acceptance.

Cadmium in kidney cortex. In general, the results of these QC analyses were better than the corresponding ones for blood. Most of the results were accepted already at an early stage according to the established criteria.

Analytical procedures. The purpose of the project was not to standardize analytical procedures. Each laboratory could use methods of its own choice, provided the produced results were accepted.

As a rule, the participating laboratories used atomic absorption spectrophotometry (AAS) with background correction. The AAS methods used for analysis of lead and cadmium in blood included the Delves Cup technique (Delves, 1970; Ediger and Coleman, 1972, 1973; Ulander and Axelson, 1974) modified according to Lind (1983a), electrothermal atomization according to Fernandez (1975), Stoeppler and Brandt (1980) or Lind (1983b), or modifications of these. For cadmium in kidney cortex all laboratories used flame AAS with dry ashing pretreatment (Kjellström *et al.*, 1974; Elinder *et al.*, 1976) or wet digestion pretreatment (Gorsuch, 1970). The methods used at each laboratory as well as the analytical performance and the problems encountered at the different laboratories have been dealt with in detail in the full report to UNEP/WHO (Vahter, 1982).

Monitoring Phase

Lead and cadmium in blood: monitoring data. The concentrations of lead and cadmium in blood given in Tables 1 and 2, respectively, are expressed as geometric means (GM) and geometric standard deviations (GSD) for the total number of subjects in each group as well as for males and females subdivided with regard to smoking habits. The geometric means and standard deviations are derived from the distribution of the logarithms of the original data and transformed back to common units. In cases where data have been reported to be below the detection limit of the analytical method, half the detection limit has been used in the statistical calculations. Sweden did not officially participate in the project, but data referring to a random sample of the population in Stockholm have been included for comparison. Data for the different subgroups, including median values, 90-percentiles, arithmetic mean values, standard deviations, geometric mean values, and geometric standard deviations for each country are given in the full report (Vahter, 1982).

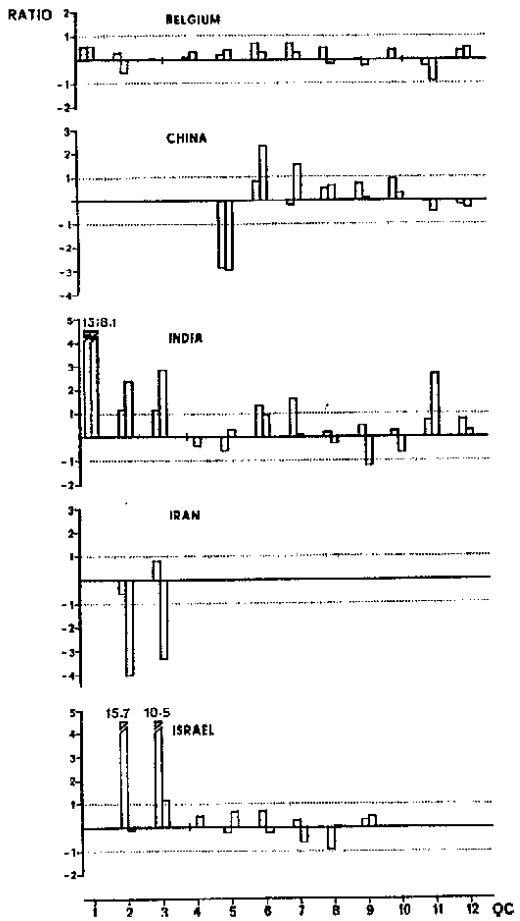


FIG. 4. Results of analysis of lead in blood for quality control runs 1–12 (training phase) expressed as ratios between calculated and accepted deviations from "true" values. The QC runs are presented in the order they have been analyzed. Dotted lines represent the acceptance interval. For further explanation, see text.

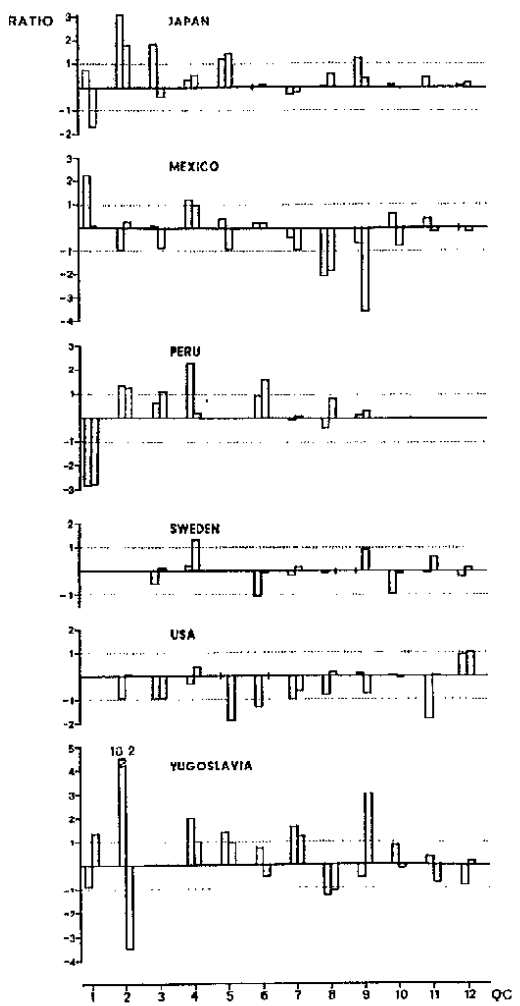


FIG. 4.—*Continued.*

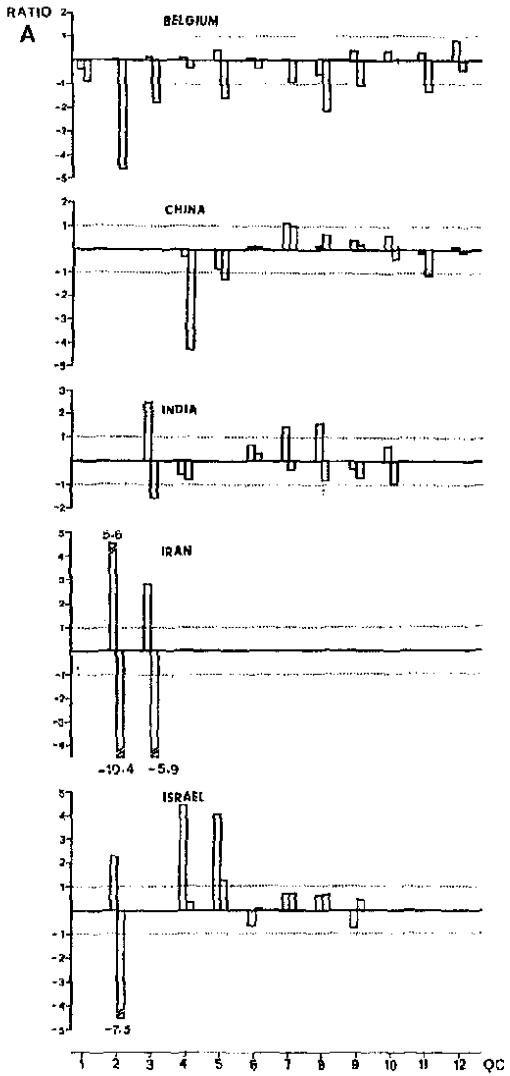


FIG. 5. Results of analysis of cadmium in blood for quality control runs 1–12 (training phase) expressed as ratios between calculated and accepted deviations from "*true*" values. The QC runs are presented in the order they have been analyzed. Dotted lines indicate the acceptance interval. For further explanation, see text.

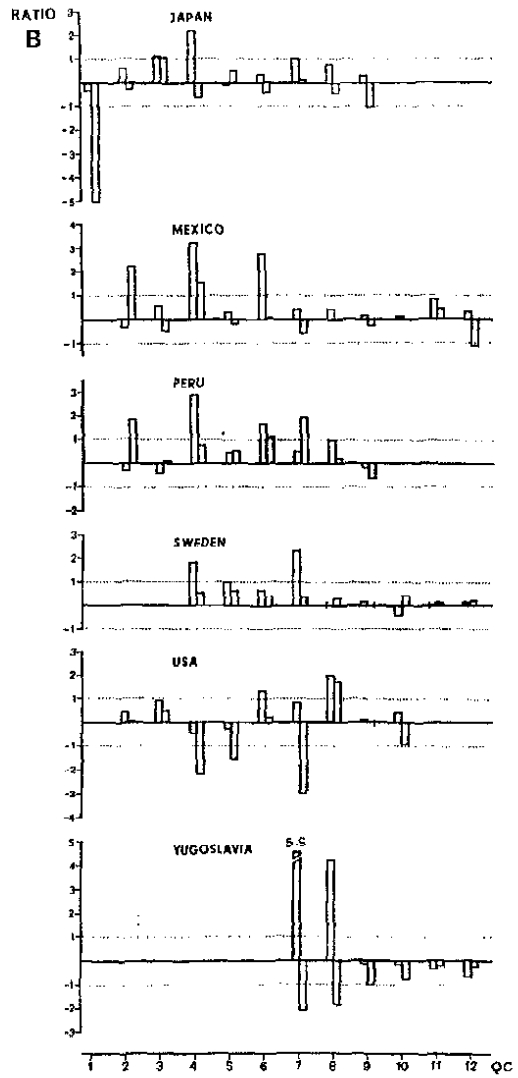


FIG. 5.—*Continued.*

TABLE 1
LEAD IN BLOOD (μg Pb/LITER) OF TEACHERS[a]

Country/area		Males N[b]	Males F	Males C	Females N	Females F	Females C	Males and females N + F + C
Belgium	GM	160	177	176	119	217	141	150
Brussels	GSD	1.3	1.2	1.2	1.3	—	1.4	1.3
	n	50	7	29	39	1	15	143[c]
China	GM	68	70	77	56	—	57	64
Beijing	GSD	1.3	1.4	1.3	1.4	—	1.4	1.4
	n	43	9	68	118	0	2	240
India	GM	141	197	131	133	—	—	138
Ahmedabad	GSD	1.5	1.9	1.5	1.6	—	—	1.6
	n	76	7	17	100	0	0	200
India	GM	224	169	160	178	—	—	179
Bangalore	GSD	1.4	1.6	1.7	1.6	—	—	1.6
	n	9	7	13	44	0	0	73
India	GM	110	145	108	104	—	—	107
Calcutta	GSD	1.7	1.4	1.3	1.3	—	—	1.4
	n	31	3	16	50	0	0	100
Israel	GM	89	104	98	64	—	74	82
Jerusalem	GSD	1.4	1.3	1.3	1.6	—	1.6	1.5
	n	92	4	37	51	0	17	201
Japan	GM	65	62	69	52	50	64	60
Tokyo	GSD	1.3	1.2	1.3	1.3	1.2	1.5	1.4
	n	17	19	64	77	8	15	200
Mexico[d]	GM	259	268	267	193	196	224	225
Mexico City	GSD	1.3	1.1	1.3	1.3	1.1	1.4	1.4
	n	21	2	13	33	2	14	85
Peru	GM	111	102	119	92	95	97	96
Lima	GSD	1.3	1.3	1.3	1.2	1.3	1.3	1.3
	n	12	24	9	89	52	20	206
Sweden[e]	GM	75	85	85	59	60	72	72
Stockholm	GSD	1.6	1.4	1.4	1.6	1.6	1.5	1.5
	n	31	31	42	45	19	42	212
United States	GM	83	97	121	62	73	73	75
Baltimore	GSD	1.4	1.3	1.5	1.4	1.5	1.5	1.5
	n	24	11	20	64	21	39	180[f]
Yugoslavia	GM	129	100	150	76	87	81	92
Zagreb	GSD	1.4	1.3	1.6	1.5	1.3	1.3	1.6
	n	30	3	27	84	3	45	192

[a] Geometric mean (GM) values, geometric standard deviations (GSD), and number of teachers (*n*) in each group indicated.
[b] N = nonsmoker, F = former smoker, C = current smoker.
[c] Includes a few with unknown smoking habits.
[d] Including 50 samples analyzed at CI.
[e] Not officially participating. Random sample of the total population.
[f] Includes one with unknown sex.

TABLE 2
CADMIUM IN BLOOD (μg Cd/LITER) OF TEACHERS[a]

Country/area		Males N[b]	Males F	Males C	Females N	Females F	Females C	Males and females N + F + C
Belgium	GM	1.0	0.9	2.1	0.9	0.7	2.2	1.2
Brussels	GSD	1.64	1.58	2.00	1.72	—	1.77	1.95
	n	50	7	29	39	1	15	143[c]
China	GM	0.5	0.8	1.8	0.7	—	2.5	0.9
Beijing	GSD	1.88	2.74	1.63	1.77	—	1.45	2.10
	n	43	9	68	118	0	2	240
India	GM	0.9	0.9	1.0	0.8	—	—	0.9
Ahmedabad	GSD	1.46	1.58	1.40	1.50	—	—	1.48
	n	76	7	17	100	0	0	200
India	GM	0.8	0.7	0.9	0.8	—	—	0.8
Bangalore	GSD	1.94	1.25	1.63	1.50	—	—	1.55
	n	9	7	13	44	0	0	73
India	GM	0.8	0.6	0.6	0.7	—	—	0.7
Calcutta	GSD	1.45	1.27	1.46	1.52	—	—	1.49
	n	31	3	16	50	0	0	100
Israel	GM	0.4	0.2	1.1	0.4	—	1.2	0.5
Jerusalem	GSD	1.80	1.00	2.72	1.81	—	2.69	2.39
	n	92	4	37	51	0	17	201
Japan	GM	0.9	1.1	1.5	1.1	1.0	1.3	1.2
Tokyo	GSD	1.66	1.55	1.55	1.62	1.42	1.84	1.64
	n	17	19	64	77	8	15	200
Mexico[d]	GM	0.3	4.2	2.6	0.3	2.1	2.1	0.7
Mexico City	GSD	3.49	1.45	3.31	3.20	—	2.99	4.65
	n	17	2	12	30	1	13	75
Peru	GM	0.6	1.2	2.5	0.8	0.9	1.4	0.9
Lima	GSD	1.53	1.89	1.95	1.50	1.58	2.05	1.78
	n	12	24	9	89	53	20	207
Sweden[e]	GM	0.1	0.3	1.6	0.3	0.3	1.5	0.5
Stockholm	GSD	1.99	2.53	2.44	1.99	1.88	1.75	3.27
	n	31	31	42	45	19	42	212
United States	GM	0.6	0.8	1.2	0.5	0.4	0.8	0.6
Baltimore	GSD	1.89	1.97	2.13	1.85	2.37	2.22	2.18
	n	24	11	20	64	21	39	180[f]
Yugoslavia	GM	0.5	0.6	3.2	0.4	0.5	2.6	0.9
Zagreb	GSD	2.11	2.36	2.54	2.07	2.35	2.68	3.43
	n	30	3	27	84	3	45	192

[a] Geometric mean (GM) values, geometric standard deviations (GSD), and number of teachers (*n*) in each group indicated.
[b] N = nonsmoker, F = former smoker, C = current smoker.
[c] Includes a few with unknown smoking habits.
[d] Including 50 samples analyzed at CI.
[e] Not officially participating. Random sample of the total population.
[f] Includes one with unknown sex.

As seen from Table 1 the spread in blood lead levels among the countries was considerable. The GM values for the total number of teachers ranged from about 60 μg Pb/liter in Beijing and Tokyo to 225 μg Pb/liter in Mexico City. The values were below 100 μg Pb/liter also in Baltimore, Jerusalem, Lima, Stockholm, and Zagreb, and between 100 and 200 μg Pb/liter in Brussels and the Indian cities. The GM plus 1.28 times GSD (calculated according to standard procedures on the logarithmic values), corresponding approximately to the 90-percentiles, ranged from 92 μg Pb/liter in Tokyo to 346 μg Pb/liter in Mexico City. In general, there was a very good agreement between geometric mean values and median values. The arithmetic mean values were slightly higher.

Males showed in general higher blood lead levels than females. On an average, the blood lead levels of male teachers were about 30% higher than those of female teachers, independent of smoking habits. Furthermore, except for male teachers in the Indian cities, smokers had somewhat higher blood lead values than nonsmokers. The differences were about the same for male and female teachers. On an average the values for smokers were about 10% higher than those for nonsmokers.

In Brussels, blood samples were collected from 179 blood donors in addition to teachers. The overall GM value and the GM plus 1.28 times GSD for teachers (150 and 210 μg Pb/liter, respectively) were about the same as those for blood donors (149 and 229 μg Pb/liter, respectively). Within the population studied in Sweden there were 15 teachers. The value for lead in blood was 90 μg Pb/liter, which should be compared with a value of 72 μg Pb/liter for the total population studied. The combined results indicate that the teachers did not differ substantially from the general population with regard to lead exposure.

As seen in Table 2 the geometric mean blood cadmium levels for the total number of subjects in the different areas ranged from 0.5 μg Cd/liter in Jerusalem and Stockholm to 1.2 μg Cd/liter in Brussels and Tokyo. The GM plus 1.28 times GSD ranged from 1.0 μg Cd/liter in Calcutta to about 5 μg Cd/liter in Mexico City. As was the case for lead in blood there was good agreement between geometric means and median values. However, the arithmetic means were often considerably higher indicating a skewed distribution of the blood cadmium levels.

There was no obvious difference in blood cadmium levels between nonsmoking males and nonsmoking females. Except for the Indian teachers and the female teachers in Tokyo, smokers showed considerably higher cadmium values than nonsmokers. Geometric mean values for nonsmokers ranged from 0.5 μg Cd/liter or less in Baltimore (female teachers), Beijing (male teachers), Jerusalem, Mexico City, Stockholm, and Zagreb to about 1 μg Cd/liter in Brussels and Tokyo. The values for smokers ranged from 0.6 μg Cd/liter in Calcutta to 3.2 μg Cd/liter among male teachers in Zagreb. On an average current smokers had about four times higher blood cadmium values than nonsmokers. Values of GM plus 1.28 times GSD in the range 5–10 μg Cd/liter for smokers were found in Brussels, Lima, Mexico City, Stockholm, and Zagreb.

Blood cadmium levels of blood donors in Brussels (1.7 μg Cd/liter) were somewhat higher than those for teachers (1.2 μg Cd/liter). The blood cadmium value of the 15 teachers from Stockholm was 0.4 μg Cd/liter which should be compared with the mean value of 0.5 μg Cd/liter for the total group studied.

Lead and cadmium in blood: quality control analysis. Sets of QC samples (as a rule five sets of six samples) were run in parallel with the monitoring to enable evaluation of the accuracy of the final results. The empirical regression lines were based on all these QC samples. The data on lead and cadmium in blood reported from Mexico (35 for lead in blood and 25 for cadmium in blood) were accompanied by one set of QC results. The 50 samples analyzed at the CI were run in parallel with two accepted QC sets.

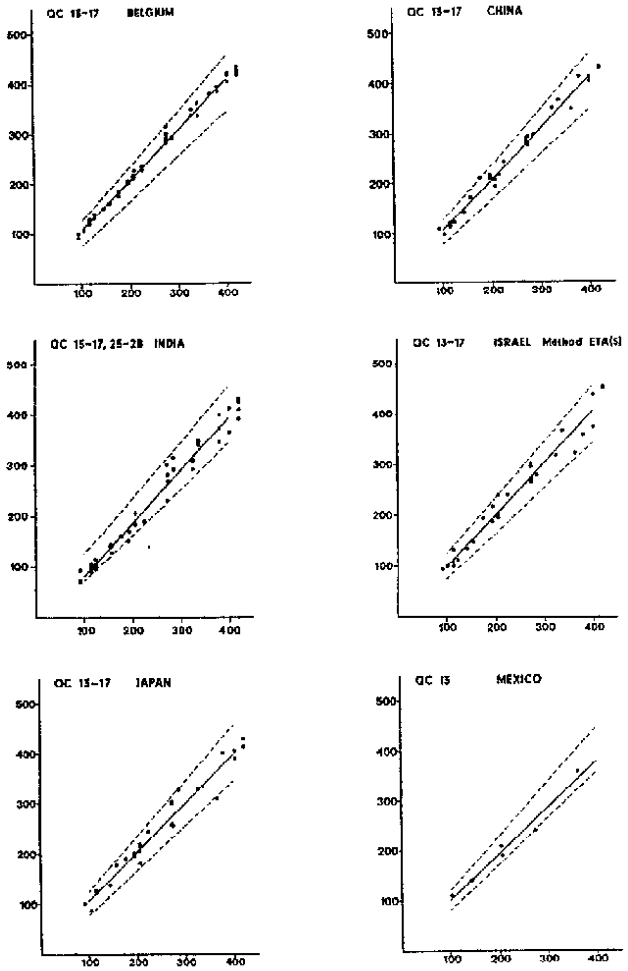
Figures 6 and 7 show the QC results from the participating laboratories. All regression lines, except that for cadmium from Mexico, were within the acceptance intervals indicating that the mean values of lead and cadmium in blood obtained by the respective laboratories were valid. The regression line for the Mexican QC results on cadmium was only slightly outside the acceptance interval and the analysis was considered satisfactory based on the previous QC runs (see Fig. 5). Furthermore, the results of the monitoring were checked by duplicate analysis at the CI (see below).

As can be seen from Figs. 6 and 7, there was often a considerable spread of the points around the regression lines. Table 3 shows the errors of method as reflected by the results from the quality control analysis. As a rule, the errors for cadmium were about the same as could be expected in laboratories performing well (0.5 μg Cd/liter). For lead, an error of method of 10 μg Pb/liter was used in the statistical evaluations. Table 3 shows that the errors at the participating laboratories varied from 8 to 31 μg Pb/liter, which has to be considered when evaluating individual values and standard deviations.

As additional quality control, some duplicate analyses were performed at the CI. Samples were randomly selected from all 200 Japanese blood samples, from the 35 samples analyzed in Mexico, and from the first 50 Peruvian samples. Table 4 shows that the agreement between values obtained at the laboratories and at the CI was good. The Mexican lead values showed a fairly wide concentration range. It was possible to compare the values obtained by the CI with those obtained by the Mexican laboratory in more detail. In Fig. 8 the CI values are plotted on the x axis and those from the laboratory in Mexico City on the y axis. It can be seen that there is a good agreement over the whole concentration range.

Cadmium in kidney cortex. The studies on cadmium in kidney cortex were carried out in the same cities as those on lead and cadmium in blood except for Belgium where the kidney cortex samples were collected in Liège. Data on cadmium in kidney cortex were not reported from Mexico and Peru. The Swedish data are from an earlier study in Stockholm (Elinder *et al.*, 1976).

Concentrations of cadmium in kidney cortex, shown in Table 5, are given in relation to age and expressed as geometric mean values (GM) and standard deviation of the geometric means (GSD). The concentrations of cadmium in kidney cortex varies with age. In general, the highest concentrations were found in the age group 40–59 years, while younger and older subjects had lower levels. Figure 9 shows a comparison of the mean cadmium levels of the 40–59 year age group in the different countries. For China all subjects over 40 years of age were included in order to increase the number of subjects. Results on subjects 40–59 years of age from the three Indian cities were pooled for the same reason. The levels varied from about 19–25 mg Cd/kg wet wt in Baltimore, Beijing, Jerusalem, Stock-



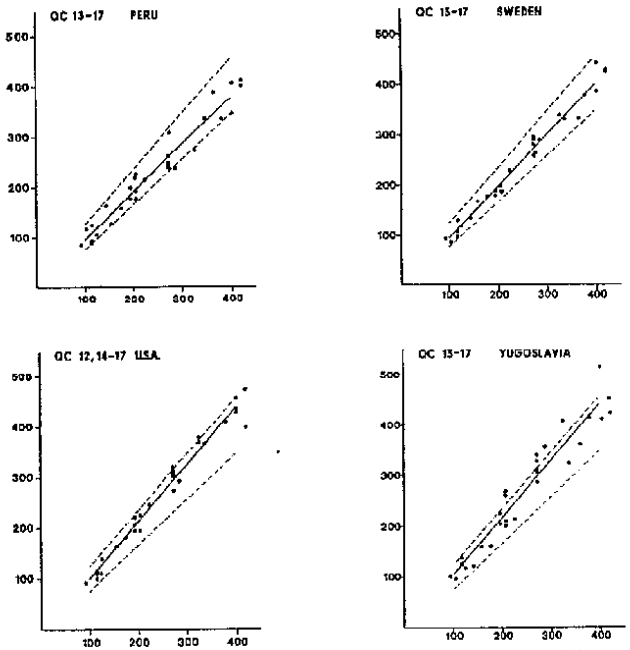
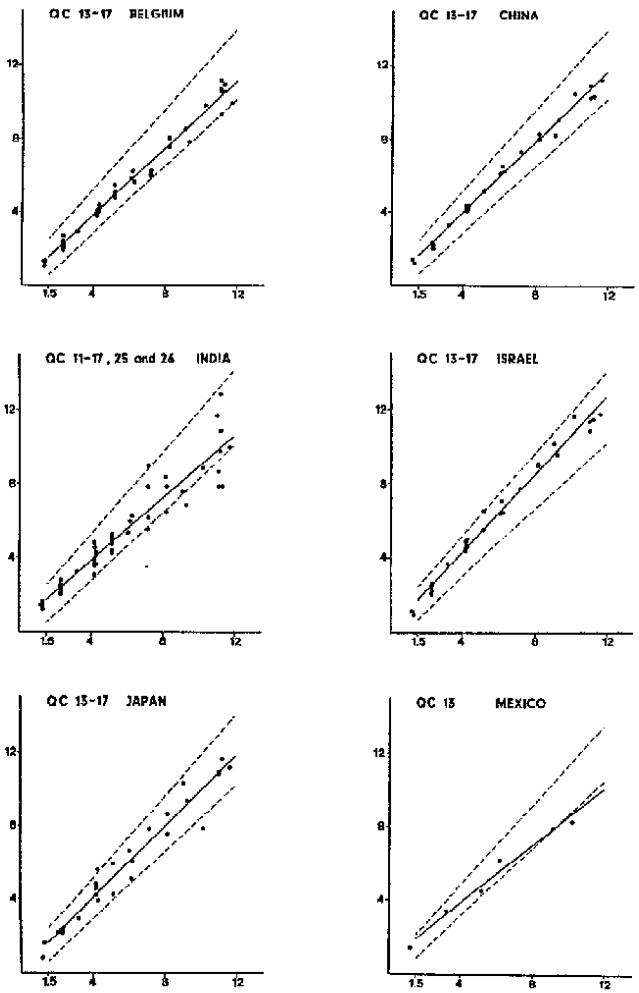


FIG. 6. Results on lead in blood (μg Pb/l) for QC samples analyzed together with the monitoring samples. *y* axis: reported values, *x* axis: reference values. Solid line is calculated regression line. Dotted lines indicate acceptance interval.

holm, and the Indian cities, to as much as 64 mg Cd/kg in Tokyo. Subjects in Liège and Zagreb had 30–40 mg Cd/kg. The values for GM plus 1.28 times GSD ranged from about 30 mg Cd/kg wet wt in China and India to about 110 mg Cd/kg wet wt in Japan.

The number of subjects in each age group was generally too low to allow a comparison between males and females. Therefore the geometric mean for all males was compared with that for all females in each city, taking into consideration the age structure. The cadmium levels in kidney cortex were not systematically related to sex.

In some countries it was possible to obtain enough information on smoking habits to allow a comparison between smokers and nonsmokers. Data for smokers and nonsmokers within the age range 30–69 years from Belgium, India (pooled data from Ahmedabad, Bangalore, and Calcutta), Japan, and Yugoslavia are presented in Fig. 10. The data indicate that smokers in general have higher values than nonsmokers, which is in accordance with the results on cadmium in blood. In India there was no obvious difference between smokers and nonsmokers with



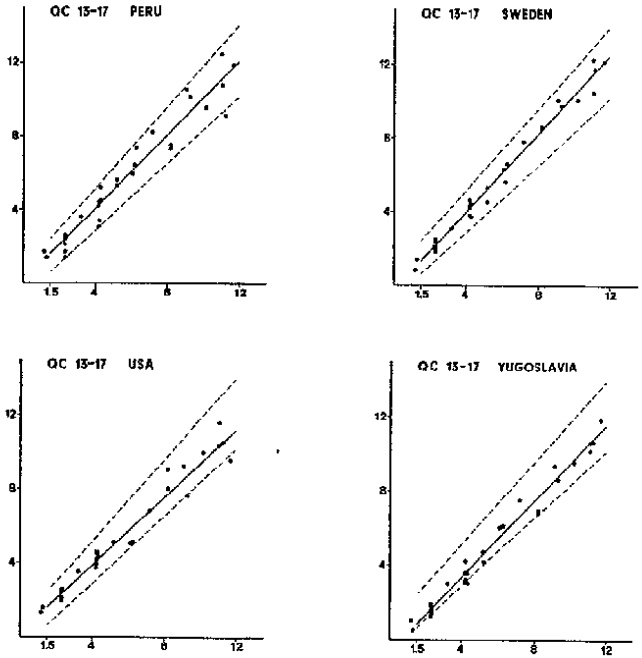


FIG. 7. Results on cadmium in blood (μg Cd/l) for QC samples analyzed together with the monitoring samples. *y* axis: reported values, *x* axis: reference values. Solid line is calculated regression line. Dotted lines indicate acceptance interval.

TABLE 3
ERROR OF METHOD FOR ANALYSIS OF QUALITY CONTROL SAMPLES (AS A RULE 30 QC SAMPLES) DURING THE MONITORING PHASE[a]

Country	Lead in blood (μg/l)	Cadmium in blood (μg/l)
Belgium	8.4	0.4
China	12.5	0.3
India	17.8	0.9
Israel	20.5	0.4
Japan	18.8	0.7
Mexico[b]	15.3	0.4
Peru	23.0	0.8
Sweden	15.2	0.4
United States	18.1	0.6
Yugoslavia	30.7	0.5

[a] Values used in the statistical evaluations were 10 μg/liter for lead and 0.5 μg/liter for cadmium.
[b] Calculated from one QC set (6 samples).

TABLE 4
COMPARISON OF RESULTS OF LEAD AND CADMIUM IN TEACHERS' BLOOD OBTAINED AT THE PARTICIPATING LABORATORIES AND THE CI

	Lead						Cadmium				
		Participating lab.		CI				Participating lab.		CI	
Country	*N*	$\bar{x}$	SE	$\bar{x}$	SE	*r*	*N*	$\bar{x}$	SE	$\bar{x}$	SE
Japan	15	64	3.6	62	4.4	0.88	15	1.3	0.13	1.4	0.15
Mexico	23	234	17.1	239	18.1	0.75	11	1.7	0.48	1.3	0.42
Peru	15	99	5.2	103	7.5	0.92	15	1.3	0.26	0.8	0.23

Note. The figures represent mean values (μg/l) and standard errors of mean (μg/l) based on analyses of a number of samples from teachers. The correlation coefficient, *r*, for lead is also given. For cadmium this parameter has not been included as the monitoring values are close to detection limit and the error of method large relative to the range of values.

regard to cadmium in kidney cortex, nor was there any major difference between smokers and nonsmokers with regard to cadmium in blood.

Three sets (in some cases more) of quality control samples were analyzed together with the monitoring samples for evaluation of the accuracy of the final results. As for blood, the QC results were plotted against the reference values. The empirical regression lines were within the acceptance intervals for all laboratories. The results of the QC analysis are given in the full report (Vahter, 1982).

DISCUSSION AND CONCLUSIONS

The project has involved design and implementation of a program for quality control, technical advice and training, and implementation of a number of studies

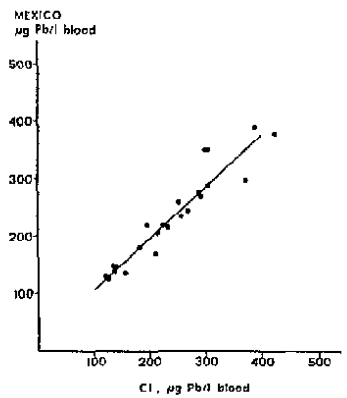


FIG. 8. Comparison between results on lead in blood obtained at CI and the laboratory in Mexico City.

TABLE 5
CADMIUM IN KIDNEY CORTEX (mg/kg WET WT)[a]

		Age (years)						
Country/area		≤19	20–29	30–39	40–49	50–59	≥60	Total
Belgium	GM	9.0	16.9	20.8	39.3	38.4	29.7	30.5
Liège	GSD	1.3	1.8	1.7	1.7	1.6	1.8	1.8
	n	4	2	11	16	35	89	158[b]
China	GM	12.6	12.4	10.3	19.0	12.0	25.7	13.0
Beijing	GSD	1.4	1.4	1.5	1.1	—	1.8	1.5
	n	2	13	6	2	1	2	26
India	GM	15.5	18.5	18.6	15.7	22.6	8.5	17.8
Ahmedabad	GSD	1.4	1.3	1.3	1.4	1.2	—	1.4
	n	4	23	14	7	2	1	51
India	GM	4.4	9.1	10.3	24.5	20.9	13.0	9.0
Bangalore	GSD	1.9	1.6	2.3	—	1.5	1.6	2.1
	n	10	11	11	1	3	6	42
India	GM	19.0	16.0	13.2	18.4	24.1	14.8	16.2
Calcutta	GSD	1.1	1.6	1.7	1.8	1.3	2.0	1.7
	n	2	10	10	11	2	4	39
Israel	GM	6.2	15.5	23.9	25.6	22.9	13.3	15.1
Jerusalem	GSD	2.0	1.6	1.7	2.3	2.1	1.6	2.0
	n	7	10	7	3	8	16	51
Japan	GM	—	25.0	59.9	67.0	61.1	61.8	56.2
Tokyo	GSD	—	1.6	1.5	1.5	1.6	1.4	1.7
	n	0	6	6	12	11	15	50
Sweden[c]	GM	5.1	10.6	18.0	21.7	18.3	12.0	13.1
Stockholm	GSD	1.9	1.9	1.9	1.8	2.3	2.0	2.0
	n	31	32	34	40	43	111	291
United States	GM	32.9	17.1	35.2	29.2	23.9	38.5	26.1
Baltimore	GSD	5.0	2.4	1.8	1.2	1.7	1.3	2.0
	n	2	8	3	3	7	3	29[d]
Yugoslavia	GM	8.0	14.8	17.9	32.6	30.7	20.0	24.2
Zagreb	GSD	—	2.6	1.9	1.8	1.8	1.9	2.0
	n	1	6	4	13	15	11	50

[a] Geometric mean (GM) values, geometric standard deviation (GSD), and number of samples in each group (*n*) indicated.
[b] Including one with unknown age.
[c] Data from Elinder *et al.* (1976).
[d] Including three with unknown age.

on exposure to lead and cadmium in certain groups in different countries. In the following, the results are discussed under two main headings, the training phase and the monitoring phase.

Training Phase

The need for a rigid quality assurance program, particularly for the measurements of lead and cadmium in blood, was confirmed by the results of the

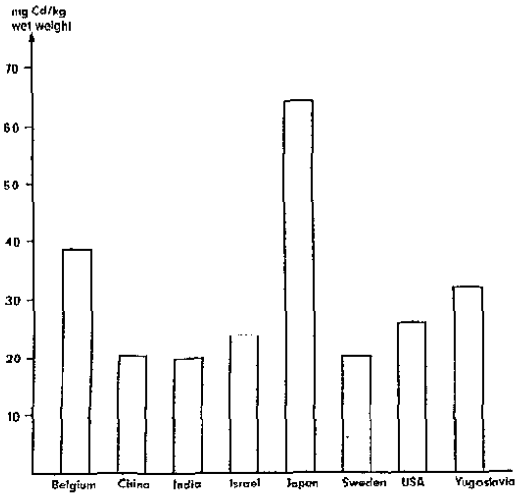


FIG. 9. Concentration of cadmium in kidney cortex (geometric mean values) for the age group 40–59 years of the population studied in the different countries. For Beijing, China, all subjects above 40 years have been included and for India data from Ahmedabad, Bangalore, and Calcutta have been pooled in order to increase the number of subjects. Swedish data from Elinder *et al.* (1976). The number of subjects in each group is given in Table 5.

quality control analyses. It was rare that a laboratory met the criteria for acceptance throughout the entire training phase of the project. In several cases problems were identified at an early stage and considerable improvement was achieved. There are data, however, which indicate that certain problems remained despite repeated consultant's visits and training. In developing countries, such problems were partly due to difficulties in obtaining spare parts and service from instrument manufacturers. Analysis of cadmium in kidney cortex was in general carried out without any major problems, mainly due to the high concentration.

It is obvious from the results of the QC analyses that an accepted performance in a limited number of quality control runs was no guarantee for a continuous good performance. Furthermore, correct results reported for the internal quality control samples did not guarantee accurate analysis of the external quality control samples. This emphasized the need to include external quality control samples also in the monitoring phase of the project.

The problems encountered within the present program are not surprising considering the difficulties in trace metal analysis and results of earlier interlaboratory comparisons. Unfortunately, however, it is still more an exception than the rule to include valid quality assurance data when publishing results from trace metal

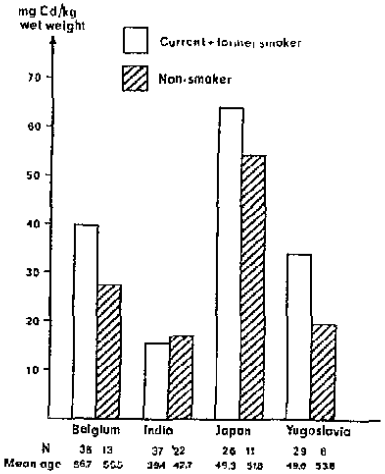


FIG. 10. Concentration of cadmium in kidney cortex (geometric mean values) in relation to smoking habits among the subjects (30–69 years of age) studied in Belgium, India (data from Ahmedabad, Bangalore, and Calcutta pooled), Japan, and Yugoslavia. Number of subjects (N) and mean age of subjects in each subgroup are indicated under the bars.

analysis. A general reference to participation in intercalibration program does not in itself assure the accuracy of presented monitoring data.

Preanalytical quality control, primarily avoidance of contamination, is another important component of all monitoring programs. A formal check of the extent to which a high standard in this respect could be maintained was not possible to carry out. Several measures were taken to avoid the risks for contamination, and hence the risk for errors due to this and similar factors has probably been brought down to a minimum. It is still not possible to exclude that occasionally, individual high values could to some extent have been caused by contamination. It seems highly unlikely, however, that such factors have to any major extent influenced the results.

The procedure for evaluation of QC data used in the present program is based on a linear regression model, which guaranteed with a certain power, that the performance of a laboratory met certain predetermined criteria. It was used primarily because this model lends itself to making probability statements in terms of statistical power. Another way is to calculate all differences between y and x along the tested range and stipulate a criterion for how large these differences could be. The latter method has been employed within the CEC monitoring project of lead (CEC, 1981). It would be desirable to evaluate different methods for

quality control criteria and their suitability for different types of monitoring programs.

Monitoring Phase

Data from the present program constitute the only comparison on a global scale of lead and cadmium concentrations in blood and cadmium in kidney cortex where a rigid quality assurance program has been implemented. The results of the quality control analysis, run in parallel with the actual monitoring of the target populations, together with a "preanalytical" quality control program makes it highly probable that the results are valid and comparable. Furthermore, the target populations studied seem to be comparable with the general population with regard to exposure to lead and cadmium, thus making an international comparison meaningful.

The results show that the exposure to lead and cadmium varied substantially among the areas studied. For lead in blood the geometric mean values thus ranged from about 60 μg Pb/liter for teachers in Beijing and Tokyo to 225 μg Pb/liter for teachers in Mexico City. The values were below 100 μg Pb/liter also in Baltimore, Jerusalem, Lima, Stockholm, and Zagreb and between 100 and 200 μg Pb/liter in Brussels and the Indian cities.

The results may be compared with those of the CEC project on lead in blood (CEC, 1981), where quality assurance procedures were also applied. The data in the CEC project are reported as median and 90-percentile values, which would be comparable with the geometric mean values (GM) and GM plus 1.28 times GSD (calculated according to standard procedures on the logarithmic values), respectively, in the present project. It is clear that most groups studied within the UNEP/WHO project had considerably lower values than was usually found within the CEC. The overall median value for the CEC survey was 130 μg Pb/liter (Berlin, 1982), and the median values for the different cities studied ranged from 100 to 210 μg Pb/liter for males and from 80 to 160 μg Pb/liter for females. The mean 90-percentiles were 245 μg Pb/liter for males (range 159–380 μg Pb/liter) and 181 μg Pb/liter for females (range 120–230 μg Pb/liter).

The reason for the large differences among the areas studied is not known. Since it is likely that the samples are comparable and that the differences are real, it is an urgent task for future programs to investigate such differences. Food and drinking habits, and use of lead in gasoline may be of particular importance.

Some tendencies noticed in the present project, which are worth persuing, relate to blood lead levels and exposure to lead from gasoline. Mexico, showing the highest blood lead level, also has the highest concentration of lead in gasoline (0.9 g/liter) among the participating countries. Mexico City is furthermore a city with extremely heavy traffic. The populations studied in Beijing and Tokyo showed the lowest blood lead levels. Tokyo, like Mexico City, is a large city with heavy traffic, but almost all gasoline used at present is unleaded. Beijing is a city with low traffic intensity and, furthermore, about 75% of the gasoline used is unleaded. The other participating countries have intermediate concentrations of lead in gasoline and also intermediate blood lead levels. That lead in gasoline is an important source of exposure is supported by data from the United States, where it has been shown that a decrease in the use of leaded gasoline results in a parallel decrease in blood lead levels (Billick *et al.*, 1980; MMWR, 1982). It must be emphasized, however, that many factors, other than lead in gasoline, may have influenced the blood lead levels in the different areas. Consumption of alcohol and canned food, for example, certainly may be of importance (see e.g. Elinder *et al.*, 1983).

It would have been of great interest to compare the results of the present study with earlier published data from different countries. Unfortunately, very few reliable international comparisons exist. One study on lead in blood, also sponsored by WHO, was performed in 1967 (Goldwater and Hoover, 1967). Although this study did not include any quality assurance data a comparison between the countries studied might be reasonably valid, since the analyses were performed at one laboratory using the same method of analysis for all samples. The median blood lead values for Peru and Sweden were in fairly good agreement with those of the present project, while for some other countries the blood lead levels were considerably higher. The median value in Japan was 210 μg Pb/liter in the 1967 study compared to 60 μg Pb/liter in the present study, that for Israel 150 μg Pb/liter in 1967 and 82 μg Pb/liter in 1981, that for three areas in the United States about 180 μg Pb/liter in 1967 and 75 μg Pb/liter in 1981, and that for Yugoslavia 150 μg Pb/liter in 1967 and 92 μg Pb/liter in 1981. Thus, provided that the data from 1967 are correct, there is a general trend for decreasing blood lead levels. For the United States this is confirmed when comparing data from a nationwide study with adequate quality control (Mahaffey *et al.*, 1979; median values 130–180 μg Pb/l) with the present data for Baltimore (median value 75 μg Pb/l). A decrease in blood lead levels is further confirmed by results of another nationwide United States study (Annest *et al.*, 1982) being part of the second National Health and Nutrition Examination Survey (NHANES II). During a 4-year period (1976–1980) there was a decrease in mean blood lead levels from 158 μg Pb/l to 100 μg Pb/l. A decrease was found for both black and white races, all age groups and both sexes.

The results of the present study confirm earlier data that males have higher blood lead levels than females (see e.g. Berlin, 1982). This can partly be explained by the higher number of red blood cells and higher hemoglobin levels among males compared to females. There was furthermore a tendency towards higher blood lead levels among smokers than among nonsmokers, which is in agreement with data reported for smokers and nonsmokers in a recent British study (Shaper *et al.*, 1982).

It was agreed upon that it should not be the aim of this project to make a detailed assessment of the implications for health on the basis of the data obtained. The differences between areas, however, are of such a magnitude that it must be considered of importance from the health point of view.

The geometric mean values for cadmium in blood ranged from 0.5 μg Cd/liter in Stockholm and Jerusalem to 1.2 μg Cd/liter in Brussels and Tokyo. The levels of cadmium in blood were closely correlated to smoking habits but the values from Brussels and Tokyo were the highest also among nonsmokers. Smokers had in general considerably higher concentrations than nonsmokers while former smokers had intermediate values. The only exception was India, where no obvious difference in blood cadmium levels between smokers and nonsmokers

could be observed. Geometric mean values plus 1.28 times GSD in the range 5–10 μg Cd/liter were noticed for smokers in several countries. It can be mentioned that a value of 10 μg Cd/liter in blood has been considered as an individual critical level for the development of low-molecular-weight proteinuria at long-term exposure (WHO, 1980b).

As could be expected based on earlier data the concentrations of cadmium in kidney cortex varied with age. In general, the highest concentrations were found in subjects 40–60 years of age. The geometric mean values for these age groups varied considerably among the areas studied: from 19–25 mg Cd/kg wet wt in Baltimore, Beijing, the Indian cities, Jerusalem and Stockholm to more than 60 mg Cd/kg in Tokyo. The high levels in kidney cortex from the Japanese subjects are in agreement with earlier studies (Ishizaki *et al.*, 1970; Kitamura *et al.*, 1970; Tsuchiya *et al.*, 1972). According to a WHO Task Group (WHO, 1977) the critical level of cadmium in the kidney cortex for tubular proteinuria is probably between 100 and 300 mg Cd/kg wet wt with the most likely estimate of about 200 mg Cd/kg.

It could not be taken for granted that there should be a very good correlation between cadmium levels in blood and in kidney cortex. Blood levels reflect to a great extent recent exposure while kidney levels reflect the accumulation over many years. Nevertheless, it can be seen that the countries with the lowest cadmium levels in blood also had low kidney cortex levels. Correspondingly, in countries with rather high mean cadmium levels in blood, kidney cortex levels were also high.

In conclusion, it can be stated that the results of the present project have strongly emphasized the need for an adequate quality assurance program, also in well-established laboratories. Quality control has not been implemented very often and there are reasons to suspect that much of the published data are inaccurate. Since such data may have been used for risk assessments, it is important when reevaluating health criteria to consider quality assurance questions in detail. The results of the present study also showed that there is a considerable variation in exposure to lead and cadmium among different countries. Since the project was a pilot study with a few participating countries only, it would be useful to extend biological monitoring to other areas. Such an extension should include integrated monitoring of different environmental media, e.g., food, drinking water, and air, which would give valuable data for evaluation of the reasons for enhanced levels in humans. Such studies will be of immediate importance for areas with high exposure levels. Also countries presently classified as low exposure areas will greatly benefit from such studies, since trends of rising exposure which ultimately may reach levels of direct implication for human health may be prevented.

APPENDIX: PARTICIPANTS IN THE PROJECT

Coordinating Institution

National Institute of Environmental Medicine and Karolinska Institute (Department of Environmental Hygiene), Stockholm, Sweden.

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Principal investigator:	Marie Vahter
Responsible analyst; analytical consultant to participating laboratories:	Birger Lind
Advisor in epidemiology and statistics:	Rune Cederlöf
Technical assistant:	Barbro Rahnster
Administrative assistant:	Margit Dahlquist
Data processing:	Lars Linnman

Participating Institutions

Belgium. Institute of Hygiene and Epidemiology, Ministry of Health, Brussels. Principal investigator: Pierre Bruaux; responsible analysts: Francoise Claeys-Thoreau, Genevieve Ducoffre.

India. National Institute of Occupational Health, Indian Council of Medical Research, Ahmedabad. Principal investigator: Surath Chatterjee (Director), Dinesh Parikh; responsible analysts: Chandrakant Pandya, Tushar Patel.

Iran. Institute of Endocrinology and Metabolism, Ministry of Health and Welfare, Teheran. Principal investigator: H. Ali Askari.

Israel. Institute for the Standardization and Control of Pharmaceuticals, Ministry of Health, Jerusalem. Principal investigator: Emil Weisenberg; responsible analyst: Fernanda Grauer.

Japan. Tokyo Metropolitan Research Laboratory of Public Health, Tokyo. Principal investigator: Takaaki Ishikawa; responsible analyst: Chikaharu Nagashima.

Mexico. Undersecretariat of Environmental Protection, Mexico City. Research investigator: Manuel Lopez Portillo y Ramos; deputy research investigator: Guillermo Díaz Mejía; head of laboratory: Alfredo Villacorta Argáez; analyst: Teresa Roldan Garcilazo.

People's Republic of China. Institute of Health, Chinese Academy of Medical Sciences, Beijing. Principal investigator: Zheng Xing-Quan; responsible analysts: Ji Rong-di, Lin Han-zhong.

Peru. National Institute of Nutrition, Ministry of Health, Lima. Principal investigator: Victor Hernández Pérez; responsible analysts: Adela Faching de Forton, Martha Arias, Nancy Robles.

United States. U.S. Environmental Protection Agency (EPA), Washington, D.C. Principal investigator: Frederick Kutz; responsible analyst: Aubry Dupuy, Jr.; advisor in epidemiology and statistics to the project: Joseph Carra.

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UNEP/WHO Secretariat

Francesco Sella, Director, Global Environmental Monitoring System (GEMS), United Nations Environment Programme (UNEP), Nairobi, Kenya.

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